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EXAMINER	
FORMAN, BETTY J	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/628,472
Filing Date: July 31, 2000
Appellant(s): WOLBER ET AL.

Bret Field, J.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4 January 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because the summary does not provide the passage supporting the embodiment of Claim 1. Claim 1 is drawn to an intermediate embodiment of invention wherein the single-stranded probe nucleic acids comprise a constant domain and a variable domain at the 5' end. The passage cited by Applicant teaches a narrower embodiment comprising the single-stranded probes of Claim 5 i.e. L-R-F-cV-5'. However, the embodiment of Claim 1 is much broader. This broader embodiment is illustrated in the summary (pages 4 and 5) but these illustrations are not part of the specification as filed nor are these embodiments described in the originally filed specification. In contrast, these illustrations constitute Applicant's simplification of the claimed invention. Therefore, summary of the invention does not provide a complete summary of the scope of the invention.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Prior Art of Record

4,734,363	Dattagupta et al.	3-1988
5,652,099	Conrad	7-1997
5,215,899	Dattagupta	6-1993

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Reiterated from the Previous Office Action

3. Claims 1-9 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta et al (U.S. Patent No. 4,734,363, issued 29 March 1988) and Conrad (U.S. Patent No. 5,652,099, issued 29 July 1997).

Regarding Claim 1, Dattagupta et al teach a method for producing a mixture of nucleic acid comprising providing distinct single-stranded nucleic acids immobilized on a substrate wherein the nucleic acid comprises a constant domain at the 3' end (complement to #16, Fig. 1) and a variable region at the 5' end (complement to #20, Fig. 1), hybridizing a nucleic acid (#16) to the constant domain to produce a duplex having a double-stranded region and a single-

stranded variable-region overhang, subjecting the duplex to cyclic reactions to produce a linearly amplified single-stranded nucleic acids and separating the single-stranded nucleic acids (Column 1, line 65-Column 2, line 58 and Examples 1, 5 and 6).

Conrad teaches a method for producing a mixture of nucleic acids the method comprising providing a plurality of different-sequence single-stranded nucleic acids, each comprising a constant domain at the 3' end (e.g. M13 primer site (fig. 14) and/or T7/SP6 promoter sites (fig. 23)) and a variable domain at the 5' end (i.e. vector insert and/or gene template) hybridizing nucleic acids to the constant domain to produce a duplex having a double-stranded region and a single-stranded variable-region overhang and subjecting the duplex to cyclic reactions to produce a mixture of linearly-amplified single stranded nucleic acids of differing sequences (i.e. probe cocktail)(Example 2, Column 24, line 53-Column 26, line 3).

Dattagupta et al does not teach the immobilized nucleic acids have differing sequences. However, as detailed above, Conrad teaches the similar method using nucleic acids of differing sequences whereby a "cocktail of probes" is produced for detection of different length, different number and/or different location of targets. Conrad further teaches these three different types diagnostic targets illustrate the broad importance of the probe cocktail producing (Column 28, lines 50-58). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Dattagupta et al by immobilizing additional nucleic acids of different sequences for the expected benefit of proving various types of diagnostics based and further based on the broad importance of probe cocktails as taught by Conrad (Column 28, lines 50-58).

Conrad does not teach immobilized duplexes. However, as detailed above, Dattagupta et al teach the similar method wherein the duplexes are covalently immobilized (Fig. 1). Dattagupta et al teaches their immobilized duplexes provide large-scale production of sequence-specific probes while eliminating the need for plasmids, cloning and restriction

(Column 1, lines 31-35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Conrad by immobilizing their plurality of duplexes for the expected benefit of providing large scale production of sequence-specific probes as taught by Dattagupta et al (Column 1, lines 31-35).

Hence the instantly claimed invention is obvious over Dattagupta et al in view of Conrad or alternatively over Conrad in view of Dattagupta et al.

Regarding Claim 2, Dattagupta et al teaches the method wherein the nucleic acids produced are DNA (Column 2, lines 34-54). Conrad teaches the nucleic acids produces are DNA (Column 24, lines 53-56).

Regarding Claim 3, Dattagupta et al teaches the method wherein the constant domain comprises a recognition domain (e.g. complement of #16, Fig. 1) and a linker domain (Column 2, lines 24-32). Conrad teaches the method wherein the constant domain comprises a recognition domain (e.g. M13 primer site (fig. 14) and/or T7/SP6 promoter sites (fig. 23).

Regarding Claim 4, Dattagupta et al teaches the method wherein the cycling is linear amplification (fig. 1 and Column 2, lines 34-54). Conrad teaches the method wherein the cycling is linear i.e. asymmetric synthesis (Column 24, lines 53-67).

Regarding Claim 5, Dattagupta et al teach a method for producing a mixture of nucleic acid comprising providing distinct single-stranded nucleic acids immobilized on a substrate wherein the nucleic acid has L (linker, Column 2, line 24-34)-R (e.g. complement of #16, Fig. 1)-F (e.g. complement for 3'nt of the primer whereby the polymerase extends) and a variable region at the 5' end (complement to #20, Fig. 1), hybridizing a nucleic acid (#16) to the R-F domains to produce a duplex having a double-stranded region and a single-stranded variable-region overhang, subjecting the duplex to cyclic reactions to produce a linearly amplified single-stranded nucleic acids and separating the single-stranded nucleic acids (Column 1, line 65-Column 2, line 58 and Examples 1, 5 and 6).

Conrad teaches a method for producing a mixture of nucleic acids the method comprising providing a plurality of different-sequence single-stranded nucleic acids, each comprising a R (primer complement)- F (polymerase binding site) (e.g. M13 primer site (fig. 14) and/or T7/SP6 promoter sites (fig. 23)) and a variable domain at the 5' end (i.e. vector insert and/or gene template) hybridizing nucleic acids to the constant domain to produce a duplex having a double-stranded region and a single-stranded variable-region overhang and subjecting the duplex to cyclic reactions to produce a mixture of linearly-amplified single stranded nucleic acids of differing sequences (i.e. probe cocktail)(Example 2, Column 24, line 53-Column 26, line 3).

Dattagupta et al does not teach the immobilized nucleic acids have differing sequences. However, as detailed above, Conrad teaches the similar method using nucleic acids of differing sequences whereby a "cocktail of probes" is produced for detection of different length, different number and/or different location of targets. Conrad further teaches these three different types diagnostic targets illustrate the broad importance of the probe cocktail producing (Column 28, lines 50-58). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Dattagupta et al by immobilizing additional nucleic acids of different sequences for the expected benefit of proving various types of diagnostics based and further based on the broad importance of probe cocktails as taught by Conrad (Column 28, lines 50-58).

Conrad does not teach immobilized duplexes. However, as detailed above, Dattagupta et al teach the similar method wherein the duplexes are covalently immobilized (Fig. 1). Dattagupta et al teaches their immobilized duplexes provide large-scale production of sequence-specific probes while eliminating the need for plasmids, cloning and restriction (Column 1, lines 31-35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Conrad by immobilizing

their plurality of duplexes for the expected benefit of providing large scale production of sequence-specific probes as taught by Dattagupta et al (Column 1, lines 31-35).

Hence the instantly claimed invention is obvious over Dattagupta et al in view of Conrad or alternatively over Conrad in view of Dattagupta et al.

Regarding Claim 6, Dattagupta et al teaches the method wherein the linker domain is 0-10 bases (Column 2, lines 24-33). Conrad teaches the method wherein the linker domain is 0 bases (Example 2).

Regarding Claim 7, Conrad teaches the method wherein the functional domain is RNA polymerase promoter domain (Column 25, lines 35-40).

Regarding Claim 8, Dattagupta et al teaches the method wherein the recognition domain is recognized by a restriction enzyme (Column 3, lines 1-17). Conrad teaches the method wherein the recognition domain is recognized by a restriction enzyme (e.g. *Eco R1*, Fig. 14 and Example 2).

Regarding Claim 9, Dattagupta et al teaches the method wherein the cycling is linear amplification (fig. 1 and Column 2, lines 34-54). Conrad teaches the method wherein the cycling is linear i.e. asymmetric synthesis (Column 24, lines 53-67).

Regarding Claims 21 and 22, Dattagupta et al teach a method for producing a mixture of nucleic acid comprising providing distinct single-stranded nucleic acids immobilized on a substrate wherein the nucleic acid comprises a constant domain at the 3' end (complement to #16, Fig. 1) and a variable region at the 5' end (complement to #20, Fig. 1), hybridizing a nucleic acid (#16) to the constant domain to produce a duplex having a double-stranded region and a single-stranded variable-region overhang, subjecting the duplex to cyclic reactions to produce a linearly amplified single-stranded nucleic acids and separating the single-stranded nucleic acids (Column 1, line 65-Column 2, line 58 and Examples 1, 5 and 6).

Conrad teaches a method for producing a mixture of nucleic acids the method comprising providing a plurality of different-sequence single-stranded nucleic acids, each

comprising a constant domain at the 3' end (e.g. M13 primer site (fig. 14) and/or T7/SP6 promoter sites (fig. 23)) and a variable domain at the 5' end (i.e. vector insert and/or gene template) hybridizing nucleic acids to the constant domain to produce a duplex having a double-stranded region and a single-stranded variable-region overhang and subjecting the duplex to cyclic reactions to produce a mixture of linearly-amplified single stranded nucleic acids of differing sequences (i.e. probe cocktail)(Example 2, Column 24, line 53-Column 26, line 3).

Dattagupta et al does not teach the immobilized nucleic acids have differing sequences. However, as detailed above, Conrad teaches the similar method using nucleic acids of differing sequences whereby a "cocktail of probes" is produced for detection of different length, different number and/or different location of targets. Conrad further teaches these three different types diagnostic targets illustrate the broad importance of the probe cocktail producing (Column 28, lines 50-58). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Dattagupta et al by immobilizing additional nucleic acids of different sequences for the expected benefit of proving various types of diagnostics based and further based on the broad importance of probe cocktails as taught by Conrad (Column 28, lines 50-58).

Conrad does not teach immobilized duplexes. However, as detailed above, Dattagupta et al teach the similar method wherein the duplexes are covalently immobilized (Fig. 1). Dattagupta et al teaches their immobilized duplexes provide large-scale production of sequence-specific probes while eliminating the need for plasmids, cloning and restriction (Column 1, lines 31-35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Conrad by immobilizing their plurality of duplexes for the expected benefit of providing large scale production of sequence-specific probes as taught by Dattagupta et al (Column 1, lines 31-35).

Dattagupta et al teaches subjecting the duplexes to in vitro transcription (reverse transcription) or linear amplification (Fig. 1 and Column 2, lines 41-48). Conrad teaches subjecting the duplexes to in vitro transcription (T7 transcription) or linear amplification (asymmetric) (Column 24, lines 53-56).

Hence the instantly claimed invention is obvious over Dattagupta et al in view of Conrad or alternatively over Conrad in view of Dattagupta et al.

Response to Arguments

Applicant asserts the examiner's prima facie case of obviousness is deficient because, A) the cited references have been impermissibly combined using only Applicant's disclosure and B) combining the references fails to teach or suggest the invention as claimed.

Regarding A): Applicant asserts that the '363 patent only describes a single type of template immobilized a solid support. Applicant further asserts that this is "an important feature of the asserted utility of the '363 patent in that the structure is a sensitive probe for a single nucleic acid analyte." Applicant's assertions are noted, however it is further noted that Applicant has not pointed to any teaching in the '363 patent to support the assertions. It is agreed that the'363 patent describes an embodiment using a single template. However, nowhere does the '363 patent teach, describe, or suggest the asserted utility of providing a sensitive probe for a single nucleic acid analyte. In contrast to Applicant's assertion, the '363 patent specifically teaches, "It is an object of this invention to synthesize specific nucleic acid sequence**S** on a relatively large scale" (Column 1, lines 31-33) and repeatedly suggests their method is useful for synthesis of probe**S** (e.g. Abstract, last sentence, and Column 2, lines 62-64). Furthermore, the immobilized probes of the '363 patent, which Applicant asserts is the defined utility, is specifically defined as an intermediate, not final, product as asserted (Column 1, lines 50-52).

Applicant argues that one of skill in the art would not be motivated to modify the beads of the '363 patent because then one would not be able to use the structure to detect a single

analyte. The argument has been considered but is not found persuasive because as noted above, the bead-immobilized probes are intermediate, not final products in the'363 method. Furthermore, the rejection above (reiterated from the previous office action), does not suggest one of skill would be motivated to modify the bead. In contrast, it was suggested that one of ordinary skill would be motivated to modify the probe synthesis of Dattagupta et al by immobilizing additional nucleic acids of different sequences for the expected benefit of providing various types of diagnostics based and further based on the broad importance of probe cocktails as taught by Conrad (Column 28, lines 50-58). It is further noted that while the solid support of the'363 patent is illustrated as a bead, the patent encompasses numerous and various supports e.g. paper and nylon (Column 2,lines 19-22).

Applicant argues that one of skill in the art would not have been motivated to modify the method of the'099 patent because "access of polymerase enzymes to the template nucleic acid could potentially be hindered". Applicant's assertion is noted, however, Applicant has not provided any evidence that the asserted problem would exist. Therefore, the assertion is deemed unsupported speculation.

Finally, Applicant asserts that the only motivation to combine the teaching is the present application. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In contrast to Applicant's assertion of impermissible hindsight reconstruction, the examiner has repeatedly and correctly pointed to specific motivation as taught in the art. It is

noted that Applicant has not addressed or contradicted any of the motivation provided in the body of the rejection as specifically taught in the cited prior art.

Regarding B): Applicant's first asserts that "mixture" as claimed, means "a heterogeneous composition of two or more distinct substances, e.g. two or more different nucleic acids of differing sequence, where each constituent member of the mixture is not physically separated from other constituents of the mixture. Applicant assets that because the'363 patent only produces a single type of nucleic acid and their "described utility is to detect a single nucleic acid analyte using the bead bound template" one would not find any suggestion to produce a mixture. The argument has been considered but is not found persuasive because, as discussed above, the asserted utility is not supported by any citation or teaching in the'363 patent. In contrast to Applicant's assertion, the'363 patent specifically teaches "It is an object of this invention to synthesize specific nucleic acid sequence**S** on a relatively large scale" (Column 1, lines 31-33) and repeatedly suggests their method is useful for synthesis of probe**S** (e.g. Abstract, last sentence, and Column 2, lines 62-64). Furthermore, the immobilized probes and/or templates of the '363 patent are specifically identified as intermediates (not final) products as asserted (Column 1, lines 50-52).

Applicant asserts that the examiner has relied on an unsupported element of the'363 patent for a teaching of mixture and that the Final Rejection did not properly point to a teaching of mixture in the prior art. Applicant assertion is noted. However, the following passage, reiterated from above as presented in the Final Rejection provides a specific teaching of mixture, as broadly claimed and as taught by Conrad.

> Conrad teaches the similar method using nucleic acids of differing sequences whereby a "cocktail of probes" is produced for detection of different length, different number and/or different location of targets. Conrad further teaches these three different types diagnostic targets illustrate the broad importance of the probe cocktail producing (Column 28, lines 50-58). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Dattagupta

et al by immobilizing additional nucleic acids of different sequences for the expected benefit of proving various types of diagnostics based and further based on the broad importance of probe cocktails as taught by Conrad (Column 28, lines 50-58).

Therefore, in contrast to Applicant's assertion, the examiner has pointed to a teaching of mixture in the prior art and as defined by Applicant (Brief, page 12, first paragraph).

Applicant argues that if the '099 patent teaches a mixture, it is incompatible with the '363 patent in view of the purpose of the '363 patent. The argument is not found persuasive because it is based on the incorrect analysis of the defined utility of the '363 patent as discussed above.

Applicant argues that the claimed invention requires an array of distinct single-stranded probe nucleic acids of differing sequence immobilized on a substrate, which "one of skill in the art, in view of the of the specification, reads the limitation as requiring a structure that is made up of a substrate which includes the distinct nucleic acids immobilized at different and known locations on the surface of the support." Applicant's interpretation of the claim language is interesting. However, the claims are not limited to positionally distinct immobilization or immobilization at different and/or known positions. Therefore, the comments are not commensurate in scope with the claims. In contrast, the claims are drawn to a plurality of different nucleic acids immobilized on a support. As stated above, the '363 patent teaches sequence immobilization on a solid support e.g. cellulose, beads, paper, nylon (Column 2, lines 19-22 and Fig. 1) wherein the object of the '363 method is "to synthesize specific nucleic acid sequence**S** on a relatively large scale" (Column 1, lines 31-33) and the'099 patent teaches synthesis of probes wherein the synthesis produces a plurality of different probes (Column 28, lines 50-58). One of ordinary skill in the art would have been motivated to combine their teachings for the reasons discussed in the above rejection as reiterated from the Final Office Action.

Applicant asserts that because the cited references do not teach a plurality of distinct nucleic acids immobilized on a single solid support, the references fail to teach every element of the claim. The argument has been considered but is not found persuasive because it is not commensurate in scope with the claim. As stated previously, the claims are not limited to a plurality of nucleic acids immobilized to a single solid support or the same solid support. In contrast, the claims are drawn to a plurality of nucleic acids immobilized to a solid support. The'363 patent specifically teaches nucleic acid immobilization for probe synthesis (Column 1, lines 65-68). The '099 patent teaches synthesis of a plurality of probes (Column 28, lines 50-58). As such, the prior art teaches all the elements of the claim as written. And one of ordinary skill in the art would have been motivated to combine their teachings for the reasons discussed in the above rejection as reiterated from the Final Office Action.

NEW GROUNDS FOR REJECTION

These new grounds for rejection are added under 37 C.F.R. § 41.39. Applicant is advised that the revised rules require that when an examiner's answer contains a new ground of rejection, appellant must, **within two months**, either:

1. request that prosecution be reopened by filing a § 1.111 reply; or

2. requires that the appeal be maintained by filing a reply brief, to avoid *sua sponte* dismissal of the appeal as to the claims subject to the new ground of rejection.

New Grounds for Rejection Based on Applicant's Arguments using Prior Art cited in the Final Office Action of June 2004

4. Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta et al (A) (U.S. Patent No. 4,734,363, issued 29 March 1988) and Conrad (U.S. Patent No. 5,652,099, issued 29 July 1997) as applied to Claim 1 above and further in view of Dattagupta (B) (U.S. Patent No. 5,215,899, issued 1 June 1993).

Regarding Claim 10, Dattagupta et al (A) teach a method for producing a mixture of nucleic acid comprising providing distinct single-stranded nucleic acids immobilized on a substrate wherein the nucleic acid comprises a constant domain at the 3' end (complement to #16, Fig. 1) and a variable region at the 5' end (complement to #20, Fig. 1), hybridizing a nucleic acid (#16) to the constant domain to produce a duplex having a double-stranded region and a single-stranded variable-region overhang, subjecting the duplex to cyclic reactions to produce a linearly amplified single-stranded nucleic acids and separating the single-stranded nucleic acids (Column 1, line 65-Column 2, line 58 and Examples 1, 5 and 6).

Conrad teaches a method for producing a mixture of nucleic acids the method comprising providing a plurality of different-sequence single-stranded nucleic acids, each comprising a constant domain at the 3' end (e.g. M13 primer site (fig. 14) and/or T7/SP6 promoter sites (fig. 23)) and a variable domain at the 5' end (i.e. vector insert and/or gene template) hybridizing nucleic acids to the constant domain to produce a duplex having a double-stranded region and a single-stranded variable-region overhang and subjecting the duplex to cyclic reactions to produce a mixture of linearly-amplified single stranded nucleic acids of differing sequences (i.e. probe cocktail)(Example 2, Column 24, line 53-Column 26, line 3).

Dattagupta et al (A) does not teach the immobilized nucleic acids have differing sequences. However, as detailed above, Conrad teaches the similar method using nucleic acids of differing sequences whereby a "cocktail of probes" is produced for detection of different

length, different number and/or different location of targets. Conrad further teaches these three different types diagnostic targets illustrate the broad importance of the probe cocktail producing (Column 28, lines 50-58). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Dattagupta et al by immobilizing additional nucleic acids of different sequences for the expected benefit of proving various types of diagnostics based and further based on the broad importance of probe cocktails as taught by Conrad (Column 28, lines 50-58).

Conrad does not teach immobilized duplexes. However, as detailed above, Dattagupta et al (A) teach the similar method wherein the duplexes are covalently immobilized (Fig. 1). Dattagupta et al (A) teaches their immobilized duplexes provide large-scale production of sequence-specific probes while eliminating the need for plasmids, cloning and restriction (Column 1, lines 31-35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Conrad by immobilizing their plurality of duplexes for the expected benefit of providing large scale production of sequence-specific probes as taught by Dattagupta et al (A) (Column 1, lines 31-35).

Dattagupta et al (A) and Conrad do not teach using their nucleic acids as primer to make a population of target nucleic acids.

However, Dattagupta (B) teach a similar method for producing nucleic acid probes i.e. transcripts (fig. 4) comprising: providing single-stranded probe nucleic acids, contacting with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang and using the duplex to produce probes (i.e. transcripts, Column 8, lines 62-Column 9, line 16) and further comprising; employing the probes as primers in a target generation step in which target nucleic acids are produced (Column 10, lines 51-Column 11, line 4) wherein the extension provides an amplification product needed for

sensitive detection (Column 11, lines 3-4). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the probes of Dattagupta et al (A) and Conrad in a primer extension reaction as taught by Dattagupta (B) for the expected benefit of providing a quantity of amplification product as needed for sensitive detection as taught by Dattagupta (B) (Column 11, lines 3-4).

Regarding Claim 11, Dattagupta (B) teaches the method wherein the target generation step comprises template driven primer extension (Column 10, lines 51-Column 11, line 4).

Regarding Claim 12, Dattagupta (B) teaches the method wherein said target generation step produces labeled target nucleic acids (Column 10, lines 56-59).

Regarding Claim 13, Dattagupta (B) teaches the method further comprising a hybridization assay comprising contacting the generated targets of Claim 10 with immobilized targets and detecting (Column 10, lines 51-Column 11, line 4).

Regarding Claim 14, Dattagupta (B) teaches the method wherein the target is labeled via immobilization and via hybridization to the labeled amplification product (Column 10, lines 51-Column 11, line 4).

Regarding Claim 15, Dattagupta (B) teaches their method provides sensitive detection (Column 10, lines 51-Column 11, line 4) and Dattagupta (A) teaches detection utilizes washing away unbound nucleic acids prior to detection (Example 5, Column 4). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to wash unbound target prior to detection for the expected benefit of sensitive detection as desired (Column 10, lines 51-Column 11, line 4).

Response to Arguments

Applicant's arguments regarding the previous rejection have been considered but are deemed moot in view of the new grounds for rejection above.

Reiterated from Previous Office Action

Claim 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta (A) (U.S. Patent No. 4,734,363, issued 29 March 1988) and Conrad (U.S. Patent No. 5,652,099, issued 29 July 1997) in view of Dattagupta (B) (U.S. Patent No. 5,215,899, issued 1 June 1993).

Regarding Claim 23, Dattagupta et al teach a method for producing a mixture of nucleic acid comprising providing distinct single-stranded nucleic acids immobilized on a substrate wherein the nucleic acid comprises a constant domain at the 3' end (complement to #16, Fig. 1) and a variable region at the 5' end (complement to #20, Fig. 1), hybridizing a nucleic acid (#16) to the constant domain to produce a duplex having a double-stranded region and a single-stranded variable-region overhang, subjecting the duplex to cyclic reactions to produce a linearly amplified single-stranded nucleic acids and separating the single-stranded nucleic acids (Column 1, line 65-Column 2, line 58 and Examples 1, 5 and 6).

Conrad teaches a method for producing a mixture of nucleic acids the method comprising providing a plurality of different-sequence single-stranded nucleic acids, each comprising a constant domain at the 3' end (e.g. M13 primer site (fig. 14) and/or T7/SP6 promoter sites (fig. 23)) and a variable domain at the 5' end (i.e. vector insert and/or gene template) hybridizing nucleic acids to the constant domain to produce a duplex having a double-stranded region and a single-stranded variable-region overhang and subjecting the duplex to cyclic reactions to produce a mixture of linearly-amplified single stranded nucleic acids of differing sequences (i.e. probe cocktail)(Example 2, Column 24, line 53-Column 26, line 3).

Dattagupta et al does not teach the immobilized nucleic acids have differing sequences. However, as detailed above, Conrad teaches the similar method using nucleic acids of differing sequences whereby a "cocktail of probes" is produced for detection of different length, different number and/or different location of targets. Conrad further teaches these three different

types diagnostic targets illustrate the broad importance of the probe cocktail producing (Column 28, lines 50-58). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Dattagupta et al by immobilizing additional nucleic acids of different sequences for the expected benefit of proving various types of diagnostics based and further based on the broad importance of probe cocktails as taught by Conrad (Column 28, lines 50-58).

Conrad does not teach immobilized duplexes. However, as detailed above, Dattagupta et al teach the similar method wherein the duplexes are covalently immobilized (Fig. 1). Dattagupta et al teaches their immobilized duplexes provide large-scale production of sequence-specific probes while eliminating the need for plasmids, cloning and restriction (Column 1, lines 31-35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Conrad by immobilizing their plurality of duplexes for the expected benefit of providing large scale production of sequence-specific probes as taught by Dattagupta et al (Column 1, lines 31-35).

Dattagupta (A) and Conrad both teach linear amplification but they do not teach strand-displacement amplification. However, Dattagupta (B) teaches a similar method for producing single stranded nucleic acids wherein the preferred method of linear amplification is strand displacement whereby multiple cycles of amplification are provided (Column 9, lines 58-67). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the strand displacement of Dattagupta (B) to the linear amplification of Dattagupta (A) and Conrad based on the preferred teaching of Dattagupta (A)(Column 9, lines 58-67).

Response to Arguments

Applicant relies on the previous arguments regarding the combination of Dattagupta et al (A) and Conrad. The arguments have been thoroughly reviewed and discussed above. Applicant asserts that Dattagupta (B) fails to make of the deficiency in the primary references.

The argument has been considered but is not found persuasive based on discussion above regarding the primary references.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

BJ Forman
Primary Examiner
Art Unit 1634

BJ Forman, PhD
March 15, 2005

Conferees
W. Gary Jones, SPE
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